#75

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants:	PHIPPS et al.	Attorney Docket No.	Arc-2426CIP1
Serial No.:	08/952,368	Group Art Unit:	3763
Filed:	17 November 1997	Examiner:	THOMPSON, M.
Title:	Electrotransport Agent Delivery Methods and Apparatus		

APPELLANTS' BRIEF ON APPEAL

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Filed herewith in triplicate is Appellants' Brief on Appeal. The Claims on appeal are attached hereto as an Appendix A.

Requirements of 37 C.F.R. § 1.192(c)

In compliance with the requirements of 37 C.F.R. § 1.192(c), Appellants provide the following:

(1) Real Party in Interest:

The real party in interest, an assignee of the subject patent application, is Alza Corporation, Mountain View, California. The real party in interest derives its interest by mesne assignment from the inventors.

(2) Related Appeals and Interferences

No other interferences known to Appellants, the Appellants' legal representatives or assignee will be directly affected by or have a bearing on the Board's decision on this case. Appellants would point out that an appeal was filed in the parent United States case 08/483,069, which issued on 09 November 1999 as patent number 5, 983,130. In that case, a Notice of Allowance was issued after the Appeal Brief was filed and prior to the filing of an Examiner's Answer.

(3) Status of claims:

Claims 1-26 are pending in this application. Claims 1-26 have all been finally rejected on various statutory bases (no claims being indicated allowable) per the Office Action mailed on 19 June 2001.

(4) Status of Amendments:

No amendment has been filed since the 19 June 2001 Office Action noted above.

(5) Summary of Invention:

The invention relates to an electrotransport device which applies a pulsing DC current having a periodic waveform, a pulsing frequency, a duty cycle, wherein a higher efficiency state is induced in the body surface when the applied current density is greater than or equal to a critical current density (I_c)and the applied pulsing current is applied for a period of time greater than or equal to a critical time period (t_c).

(6) Issues on Appeal:

a. Whether Appellants' claims 2 and 15 are properly rejected under § 112, paragraph 2, as being indefinite because of inclusion in the claims of the term "stable" in relation to "efficiency".

b. Whether Appellants' claims 1-10 and 12-25 are properly rejected under 35 U.S.C. § 102(b) as being anticipated by Tapper (U.S. Patent No. 4,822,334).

c. Whether Appellants' claims 1-10 and 12-25 are properly rejected under 35 U.S.C. § 102(b) as being anticipated by Haak (U.S. Patent No. 5,203,768).[1]

d. Whether Appellants' claims 1-10 and 12-25 are properly rejected under 35 U.S.C. § 103(a) as being obvious over Tapper (U.S. Patent No. 4,822,334).in view of Haak (U.S. Patent No. 5,203,768).

e. Whether Appellants' claims 3-6, 12-13, 17-19 and 21-23 are properly rejected under 35 U.S.C. § 103(a) as being unpatentable over Tapper (U.S. Patent No. 4,822,334) in view of Sorenson et al. (WO 91/15258).

f. Whether Appellants' claims 11 and 26 are properly rejected under 35 U.S.C. § 103(a) as being unpatentable over Tapper (U.S. Patent No. 4,822,334) in view of Haak (U.S. Patent No. 5,203,768).

---

[1] It should be noted that in the 19 June 2001 Office Action, the Examiner did not reference a specific Haak patent. Appellant is assuming that all references to a Haak patent by the Examiner are intended as references to U.S. Patent No. 5,203,768 which was listed as Ref B in the Notice of References Cited which was included with the 19 June 2001 Office Action (paper #12).

(7) Grouping of Claims

Claims 1-26 stand or fall together.

(8) Arguments

8A. Rejection under § 112, paragraph 2

The Examiner has rejected claims 2 and 15 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellants regards as their invention. In particular the Examiner asserts that it is unclear how stability can relate to efficiency and "What about Efficiency is stable".

The present invention requires understanding of several key concepts which will now be discussed. Efficiency, as it relates to electrotransport drug delivery devices refers to the amount of drug that is delivered per unit of current that flows from one electrode through the patient and the patient's skin and back into the secondary electrode. The greater the efficiency, the greater the amount of drug delivered per the same quantity of current flow.

Another concept is that of current density, which is defined as the ratio of current to the area through which the current flows. Current density is typically expressed herein as units of microamperes/cm^2. If the same amount of current flows through a smaller area of skin, then current density would be higher. If the current density is too high, then the patient can experience pain and discomfort. Reducing current density by increasing the area of electrode contact is not necessarily a good solution. Practical engineering concerns limit the area of electrode contact. If the area of electrode contact is made larger, then there is greater cost, greater difficulty in keeping the electrode attached to the skin and a decrease in the likelihood of patient compliance due to increased discomfort for the patient.

Theoretically, the amount of drug delivered should be strictly dependent on the amount of current flow. This is because the flow of the ionic drug molecules into the skin should be directly dependent on current flow. However, the present application teaches to the contrary.

If current is applied to the skin above a certain critical current density(I_c) and for a critical time period (t_c), then efficiency is enhanced and there is less variability in efficiency if the current density changes. As disclosed on page 7, lines 14-20, of the present application, efficiency is quite variable depending upon what level current density is applied to the skin. Current densities above a certain critical value (I_c), applied for at least a critical period of time (t_c) induce a higher efficiency state and a relatively non-variable (i.e. stable) drug delivery efficiency state.

Figure 1 in the present application shows a graph with current density (expressed as $\mu A/cm^2$) displayed along the horizontal axis and drug delivery efficiency (expressed as $\mu g/mAh$) shown along the vertical axis. An inspection of Figure 1 shows that in the range of current densities below about 70 $\mu A/cm^2$ (marked as I_c on the graph), efficiency changes markedly with respect to changes in the current density. Above about 70 $\mu A/cm^2$, efficiency is much less variable and more stable with respect to changes in the current density.

Appellants assert that the language of claim 2 and 15 is clear and definite and is in compliance with § 112, paragraph 2. Appellants assert that the rejection by the Examiner of claims 2 and 15, based upon § 112, paragraph 2 should be reversed.

8B. Rejection under § 102(b) as being anticipated by Tapper

The Examiner has rejected Appellants' claims 1-10 and 12-25 under 35 U.S.C. § 102(b) as being anticipated by Tapper (U.S. Patent No. 4,822,334).

8B

i. Literal Anticipation

"Anticipation under 35 U.S.C. Section 102(b) requires the presence in a single prior art disclosure of each and every element of a claimed invention." Electro Med. Sys. S.A. v. Cooper Life Sciences, 34 F.3d 1048, 1052, 32 USPQ2d 1017, 1019 (Fed. Cir. 1994).

Tapper does not disclose delivery of current above a critical current density (I_c)and applied for a period of time greater than or equal to a critical time period (t_c)and does not disclose the induction of an enhanced efficiency state, which are all elements of Appellants' independent claims 1 and 14.

Therefore Tapper does not literally disclose a number of the elements recited in Appellants' claims and therefore cannot serve as a prior art reference for literal anticipation.

8B

ii. Inherency

Even if Tapper does not literally anticipate it might be said to anticipate based upon an argument of inherency. However, even the principle of inherency cannot be relied upon in this case, because that principle requires that the limitation must necessarily exist, even though not explicitly described.

As reaffirmed by the CAFC in *In re Robertson*, 49 USPQ2d 1949 (Fed. Cir. 1999), "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."

The Examiner has asserted that it is his "...position that these 'properties' of current and/or its density (i.e. frequency and/or pulsing frequency, duty cycle, periodic waveform) are in the least obvious if not inherently related mathematically and are within the 'critical density level' range indicated in Appellants' specification". Page 4, paragraph 7, Office Action dated 19 June 2001.

In order to claim an inherent disclosure by Tapper, *In re Robertson* requires that the elements of Appellants' claims must necessarily be an element of the Tapper disclosure, even though not explicitly stated.

Tapper does discuss a range of operational parameters, but nothing therein discloses any knowledge or awareness of critical current density and/or critical time for the purpose of achieving an enhanced efficiency state. There is nothing in Tapper which provides any support for the assertion that Tapper's device must necessarily deliver current with the proper parameters of pulsing, critical current density and critical time needed to induce the higher efficiency state. Tapper does teach a means for selectively varying the magnitude of the current in order to provide for patient comfort or convenience. Col 2, lines 58-60. However, there is nothing to indicate that varying the current for patient comfort must necessarily result in a device having all of the elements of Appellants' claims.

Therefore Tapper cannot serve as either a literal anticipatory prior art reference or an inherency based anticipatory prior art reference. Appellants respectfully request that the rejection by the Examiner under 35 U.S.C. § 102(b) based on Tapper be reversed.

8C. Rejection under § 102(b) as being anticipated by Haak

The Examiner has rejected Appellants' claims 1-10 and 12-25 under 35 U.S.C. § 102(b) as being anticipated by Haak (U.S. Patent No. 5,203,768).

The Examiner has asserted essentially the same arguments used to support the § 102 rejection based on Tapper, in support of the § 102 rejection based upon Haak.

Appellants reply with the same counter arguments. There is no literal infringement by Haak, as there is no disclosure or teaching regarding critical current densities and critical times.

In the same manner, there is no anticipation based upon inherency because Appellants' claim elements do not of necessity have to be present in the device and methods as disclosed by Haak.

Therefore Haak cannot serve as either a literal anticipatory prior art reference or an inherency based anticipatory prior art reference. Appellants respectfully request that the rejection by the Examiner under 35 U.S.C. § 102(b) based on Haak be reversed.

8D. Rejection under § 103(a) as being obvious over Tapper in view of Haak

The Examiner has rejected Appellants' claims 1-10 and 12-25 under 35 U.S.C. § 103(a) as being obvious based upon Tapper (U.S. Patent No. 4,882,334) in view of Haak (U.S. Patent No. 5,203,768).

The Examiner has not put forth a separate argument as to why Taper in view of Haak would be obvious apart from the general argument that because these references disclose power supplies having the ability vary a number of the power supply related parameters and that these parameters are in some sense mathematically convertible from one to the other. According to the

Examiner, these disclosures in combination render it obvious to provide an electrotransport device having the parameters disclosed in Appellants' claims.

But Appellants' claims require a specific combination of these parameters that are not disclosed in any fashion by the either of the two references, either alone or in combination. Nor is their any teaching that would lead one to skilled in the art to limit the enormous range of the various electrical parameters to the narrow and specific choices recited in Appellants' claims. Just because a device might be capable of delivering independently a certain current density and a certain timed pulse doesn't mean that the device is in fact capable of delivering current with both of the parameters occurring at the same time and in such a manner as to induce a higher efficiency state for a specific drug contained in specific formulation in specific configuration device.

Because the Examiner has failed to make a prima facie case of obviousness based upon the combined teachings for Tapper and Haak, Appellants respectfully request that the rejection by the Examiner under 35 U.S.C. § 103(a) over Tapper in view of Haak be reversed.

8E. Rejection under § 103(a) as being obvious over Tapper in view of Sorenson

The Examiner has rejected Appellants' claims 3-6, 12-13, 17-19, and 21-23 under 35 U.S.C. § 103(a) as being unpatentable over Tapper (U.S. Patent No. 4,822, 334) in view of Sorenson et al. (WO 91/15258).

The Examiner asserts that Tapper teaches all of the limitations of Appellants' claims 1-10, and 12-25 and that Sorenson is cited to show the teaching of DC current used in the range of 40-100 microamps.

However, even Tapper in view of Sorenson doesn't teach the combination of critical current density and critical time. Nothing in Tapper or Sorenson, alone or in combination, teaches the combination of these two factors or provides a motivation for limiting the wide range of power supply parameters to those recited in Appellants' claims.

Because the Examiner has failed to make a prima facie case of obviousness based upon the combined teachings for Tapper and Sorenson, Appellants respectfully request that the rejection by the Examiner under 35 U.S.C. § 103(a) over Tapper in view of Sorenson be reversed.

8F. Rejection under § 103(a) as being obvious over Tapper in view of Haak

The Examiner has rejected Appellants' claims 11 and 26 under 35 U.S.C. § 103(a) as being unpatentable over Tapper (U.S. Patent No. 4,822, 334) in view of Haak (U.S. Patent No. 5,203,768).

The Examiner has asserted that "...he [HAAK] further states that a therapeutic 'system' can be designed to transdermally delivery the therapeutic agent. This is construed by the Examiner to be an example of introducing competitive specie/s to the donor reservoir". Appellant believes that the Examiner has misunderstood the definition of "competitive species". As disclosed on page xx, lines xx-xx of the present application, a competitive species is a non-drug of the same ionic charge as the drug ion. This is intended as a method of controlling or reducing the delivery of drug ion without losing the enhanced state of efficiency that results from delivering current at the critical current density for the critical time. The Examiner's proposal of using a second drug that is similar to the first drug is not the use of a competitive species as disclosed in claims 11 and 26 and the disclosure.

There is no teaching in Tapper or Haak, alone or in combination, that makes obvious the use of a non-competitive ion of the same charge as the drug ion as a mean of controlling drug delivery without altering the enhanced efficiency state.

Because the Examiner has failed to make a prima facie case of obviousness based upon the combined teachings for Tapper and Haak, Appellants respectfully request that the rejection by the Examiner under 35 U.S.C. § 103(a) over Tapper in view of Haak be reversed.

9. CONCLUSION

For the all reasons set forth above, reversal of the rejections of all claims is respectfully solicited.

Dated: 23 May 2002

Respectfully submitted,

By: Owen J. Bates

Owen J. Bates

Registration No. 40,346

ALZA Corporation
1900 Charleston Road
(P.O. Box 7210)
Mountain View, CA 94303
Telephone: (650) 564-7867 Fax: (650) 564-2195

Appendix

Claims on Appeal

1. (Amended) An electrotransport device for in vivo delivery of a charged agent through a body surface at a higher electrotransport agent delivery efficiency (E) defined by the agent delivery rate per unit of applied current; the device (10) having a donor reservoir (26, 46) containing the charged agent and having a delivery area, and having a source of electrical power (32) and a current controller (19, 40), the device (10) being characterized by:

the current controller (19, 40) being adapted to provide an applied pulsing DC current having a periodic waveform, a pulsing frequency, a duty cycle, the pulsing current applied to the reservoir (26, 46) and to the body surface, wherein an applied current density is defined by the applied pulsing current divided by the delivery area, and wherein a higher electrotransport agent delivery efficiency (E) state us induced in the body surface when the applied current density is greater than or equal to a critical current density level (I_c) and the applied pulsing current is applied for greater than or equal to a critical time period (t_c).

2. The device of claim 1, wherein the agent delivery efficiency (E) is more stable when the applied current density is above the critical level (I_c) and less stable when the applied current density is below the critical level (I_c).

3. The device of claim 1, wherein the device (10) is adapted to be applied to intact human skin and the controller (19, 40) is adapted to provide an applied current density of at least about 40 $\mu A/cm^2$.

4. The device of claim 1, wherein the agent is fentanyl and the controller (19, 40) is adapted to provide an applied current density of at least about 40 $\mu A/cm^2$ for a at least about 10 msec.

5. The device of claim 1, wherein the agent is goserelin and the controller (19, 40) is adapted to vary and control the periodic current waveform to provide an applied current density of at least about 50 $\mu A/cm^2$ applied for a period of at least about 10 msec.

6. The device of claim 1, wherein t_c is at least 5 msec.

7. The device of claim 1, wherein the periodic current waveform has a current magnitude that provides a second applied current density less than I_c.

8. The device of claim 7, wherein the second applied current density is approximately zero.

9. The device of claim 7, wherein the controller (19, 40) is adapted to vary the duty cycle and the agent delivery rate.

10. The device of claim 7, wherein the controller (19, 40) is adapted to vary the frequency and the agent delivery rate.

11. The device of claim 1, wherein the donor reservoir contains at least one suitable competitive species.

12. The device of claim 1, wherein the controller (19, 40) is adapted to vary and control the frequency of the applied pulsing current to less than about 100 Hz.

13. The device of claim 1, wherein the controller (19, 40) is adapted to vary and control the frequency of the applied pulsing current to less than about 10 Hz.

14. (Amended) A method of in vivo delivery of a charged agent from an electrotransport delivery device (10) through a body surface at higher electrotransport agent delivery efficiency (E) defined by the agent delivery rate per unit of applied current; the device (10) having a donor reservoir (26, 46) containing the agent and having a delivery area, and having a source of electrical power (32) and a current controller (19, 40), the method being characterized by the

steps of:

adapting the current controller (19, 40) to provide an applied pulsing DC current having a periodic current waveform, a pulsing frequency, and a duty cycle, the pulsing current applied to the reservoir (26, 46) and to the body surface, wherein an applied current density is defined by the applied pulsing current divided by the delivery area, and wherein a higher electrotransport agent delivery efficiency (E) state is induced in the body surface when the applied current density is greater than or equal to a critical current density level (I_c) and the applied pulsing current is applied for greater than or equal to a critical time period (t_c).

15. The method of claim 14, wherein the agent delivery efficiency (E) is more stable at a current density above the critical level (I_c) and less stable at a current density below the critical level (I_c).

16. The method of claim 14, wherein the device is adapted to be applied to human skin and the controller (19, 40) provides an applied current density of at least about 40 $\mu A/cm^2$.

17. The method of claim 14, wherein the agent is fentanyl and the controller (19, 40) provides an applied current density of at least 40 $\mu A/cm^2$ for a period of at least about 10 msec.

18. The method of claim 14, wherein the pulsing frequency is less than about 100 Hz.

19. The method of claim 14, wherein the pulsing frequency less than about 10 Hz.

20. The method of claim 14, wherein the duty cycle is less than about 100%.

21. The method of claim 14, wherein the body surface comprises intact human skin and I_c is at least about 40 $\mu A/cm^2$.

22. The method of claim 14, wherein the agent is fentanyl, the body surface is human skin and the applied pulsing current is equal to I_c which is at least about 40 $\mu A/cm^2$, and wherein the pulsing current is applied for at least about 10 msec.

23. The method of claim 14, wherein the agent is goserelin and the applied pulsing current is at least about 50 $\mu A/cm^2$, and wherein the pulsing current is applied for at least about 10 msec.

24. The method of claim 14 further including the step of varying the duty cycle of the agent delivery rate.

25. The method of claim 14 further including the step of varying the pulsing frequency and the agent delivery rate.

26. The method of claim 14 further including the step of adding a suitable competitive specie to the donor reservoir (26, 46).